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Postoperative and long-term outcomes in children with Trisomy 21 and single ventricle palliation

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Abstract

Objective: Patients with Trisomy 21 (T21) and single ventricle (SV) physiology present unique challenges compared to euploidic counterparts. This study reports postoperative and long-term outcomes in patients with T21 and SV palliation.

Design: This retrospective cohort study from the Pediatric Cardiac Care Consortium (PCCC) included patients with T21 (<21 years old) that underwent surgical palliation for SV between 1982 and 2008 and control patients without known genetic anomaly following Fontan palliation for similar diagnoses. Kaplan-Meier survival plots were created based on death events obtained from the PCCC and by linkage with the National Death Index (NDI) and the Organ Procurement and Transplantation Network (OPTN) through 2014 for patients with adequate identifiers.

Results: We identified 118 children with T21 who underwent initial surgical SV palliation. Among 90 (75.6%) patients surviving their first surgery, 66 (73.3%) underwent Glenn anastomosis and 25 (27.8%) completed Fontan palliation with in-hospital survival of 80.3% and 76.0%, respectively. Fifty-three patients had sufficient identifiers for PCCC-NDI-OPTN linkage. Ten-year survival, conditioned on discharge alive after the Fontan procedure, was 66.7% compared to 92.2% for 51 controls without genetic anomaly (P = .001). Median age at death for T21 patients following initial surgical SV palliation was 2.69 years (IQR 1.34-7.12) with most deaths (89.2%) attributed to the underlying congenital heart disease (CHD).

Conclusions: Children with T21 and SV are at high risk for procedural and long-term mortality related to their genetic condition and underlying CHD. Nevertheless, a select group of patients can successfully complete Glenn or Fontan palliation, reaching satisfactory long-term survival.

KEYWORDS
congenital, Down syndrome, heart defects, retrospective studies

1 | INTRODUCTION

Trisomy 21 (T21) is the most common chromosomal abnormality associated with congenital heart disease (CHD) with 40%-50% of them carrying CHDs. In addition, T21 is frequently associated with other syndrome-specific respiratory, gastrointestinal, endocrine, and hematologic anomalies.[1] In-hospital mortality of patients with T21 following bi-ventricular repair of CHD has been reported to be similar to patients without chromosomal anomalies.[2-6] However, patients with T21 and single ventricle (SV) physiology experience

high procedural and ongoing morbidity and mortality compared to euploidic peers, mostly attributed to adverse effects of elevated pulmonary vascular resistance on the SV physiology.[4,5,7-9]

The purpose of this study is to describe in-hospital and long-term death events and causes of death in children with T21 following surgical palliation for SV. Additionally, we compare transplant-free survival following the Fontan procedure between SV patients with T21 and without a known genetic anomaly. We used the linked dataset of the Pediatric Cardiac Care Consortium (PCCC), a large multi-center registry for interventions for CHD, with the National Death Index (NDI) for information on outcomes and causes of death, and with the Organ Procurement and Transplantation Network (OPTN) for organ transplant information.[10,11]

2 | PATIENTS AND METHODS

This study was approved by the Institutional Review Board at MemorialCare Health Services, the University of Minnesota, and Emory University. Data were obtained from the PCCC, one of the oldest and largest congenital cardiac surgical and catheterization registries in the United States.[12] We queried the PCCC for patients with T21 and SV physiology who were enrolled in a US center <21 years of age between January 1, 1982 and December 31, 2008. We reviewed surgical records to validate that the patients were not candidates for bi-ventricular repair by their treating physician. Patients who underwent their initial cardiac surgery at a non-PCCC participating center were excluded to avoid immortal person-time bias.

Linkage to the NDI was possible for the subset of patients who were enrolled in the PCCC prior to April 15, 2003 (implementation date of stricter Health Insurance Portability and Accountability Act privacy rules) and had sufficient identifiers for linkage. These identifiers were submitted to the NDI to obtain information about long-term survival and cause of death up to December 31, 2014. The NDI is considered the "gold standard" of mortality and cause of death information in the United States.[13] Sensitivity of the PCCC-NDI linkage was reported to be 88.1% for death events among patients with adequate identifiers and specificity exceeded 99%.[10] Available PCCC identifiers were also submitted to OPTN to determine transplant status from January 1, 1988 (earliest available data from OPTN registry) through December 31, 2014. The OPTN data system includes data on all donor, wait-listed candidates, and transplant recipients in the United States, submitted by its members. The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the OPTN contractor. Transplant status was defined as being listed for transplant or organ transplant from PCCC report or OPTN. The sensitivity of the PCCC-OPTN linkage has been reported to be 89.7% and specificity exceeded 99%.[10]

Analysis included three treatment eras; 1982-1989, 1990-1999, and 2000-2008. Age groups at the first PCCC surgery were defined as neonatal (≤28 days), infant (29 days to 1 year), and child (>1 and <21 years). Systemic SV diagnosis was classified as (a) dominant right ventricle (RV) in cases of left ventricular hypoplasia including hypoplastic left heart syndrome; (b) dominant left ventricle (LV) in cases with RV hypoplasia including tricuspid or pulmonary atresia; (c) unbalanced common atrioventricular canal (CAVC); and (d) Other specified SV lesions identified by the treatment team as incompatible with bi-ventricular repair.

The SV physiology was classified as: (a) Stage 1, when the pulmonary flow is either controlled by a pulmonary artery (PA) band or provided by aortopulmonary (AP) shunt with or without the need for a Norwood or Damus-Kaye-Stansel (DKS) procedure, (b) Stage 2, when the pulmonary flow is provided by a superior cavo-pulmonary anastomosis (Glenn), and (c) Stage 3, when the pulmonary flow is provided by a form of total cavo-pulmonary connection (Fontan).

Pre-Fontan hemodynamic data including mean pulmonary arterial pressure (mPAP in mm Hg), transpulmonary gradient (TPG in mm Hg), pulmonary vascular resistance (PVR in WU m^2), and mixed venous oxygen saturation (SVO_2) were abstracted when available. Long-term mortality was defined as death reported in NDI following discharge after initial PCCC surgical procedure. To compare long-term survival between SV patients with T21 and those without chromosomal abnormality, we identified PCCC patients matched on anatomy and birth era with no reported genetic diagnosis, who underwent a Fontan procedure. Data collection forms and procedural reports for this comparison group were manually reviewed to exclude patients with diagnoses associated with heterotaxy, including interrupted inferior vena cava, anomalous pulmonary venous return, asplenia or polysplenia, situs ambiguous, or intestinal malrotation.

Non-parametric statistics were reported for non-normally distributed data. Groups were compared using Chi-square or Fisher's exact test as appropriate for categorical variables or Mann-Whitney *U* test for continuous variables. A P value < .05 was considered statistically significant, with Bonferroni adjustment for multiple comparisons as appropriate. Kaplan-Meier survival estimates were utilized to describe long-term survival. Follow-up duration was determined from the date of hospital discharge from the first PCCC surgical procedure through date of death, transplant, or December 31, 2014 (latest available NDI and OPTN update), whichever came first. Statistical analysis was completed using STATA version 15 (StataCorp LLC, College Station, TX) and SAS version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

A flow diagram of patient selection, exclusion, and outcomes is detailed in Figure 1. A total of 118 patients met the eligibility criteria. Characteristics of the 118 patients, comparing those with sufficient identifiers for PCCC-NDI linkage to those without sufficient identifiers are shown in Table 1. No differences were observed between groups in sex, age at first PCCC intervention, final physiologic stage, or SV diagnostic category. The majority (97/118, 82.2%) of patients had an unbalanced CAVC, with 60 (61.8%) of those with unbalanced

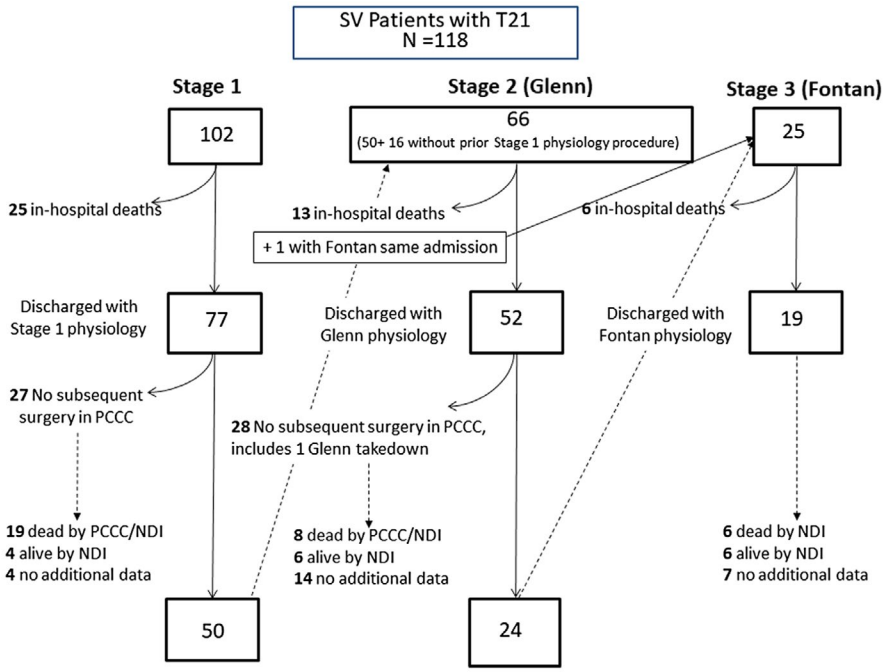

FIGURE 1 Flow diagram of the Trisomy 21 SV cohort in the Pediatric Cardiac Care Consortium (PCCC) with procedures and outcomes by physiology stage. NDI, National Death Index

CAVC having a dominant LV. After removing patients who met exclusion criteria, 53 patients (29 male, 24 female) formed our cohort for long-term survival analysis.

3.1 | Surgical procedures and outcomes

Surgical outcomes by staged physiology are presented in Table 2, while the detailed surgical procedures performed during 118 initial and 92 subsequent hospitalizations are summarized in Table 3. In-hospital mortality for all index cardiac operations was 50/210 (23.8%) and was especially high for the Norwood and DKS (alone or in combination with Glenn) procedures (17/25, 68.0%). Neonatal surgical intervention was performed in 50/118 (42.4%) patients, most commonly for controlling the pulmonary blood flow with a PA band (13/50, 26.0%) or AP shunt (17/50, 34.0%), followed by Norwood procedure in 13 patients (26.0%). In-hospital mortality following neonatal surgery was 16/50 (32.0%).

From the 102 patients who underwent an initial procedure establishing stage 1 physiology (PA band or AP shunt), 25 died in-hospital following this (24.5% mortality) and 50 reached stage 2 physiology (Glenn) in PCCC. Of the 27 patients who did not reach Stage 2, 19 died based on PCCC records and/or NDI linkage and four are presumed alive since there were no death events reported in PCCC or the NDI. For the remaining four, no information is available after their last PCCC encounter due to lack of direct identifiers for subsequent tracking (Figure 1). Sixteen patients did not undergo an initial stage 1 physiology procedure.

The 50 survivors of stage 1 palliation that were deemed eligible for a second stage procedure (Glenn), along with 16 patients without prior surgery, formed the group that underwent Glenn procedure at a median age of 9.3 months (IQR 6.2-14.4 months). Of the 52 survivors discharged with Glenn physiology plus one patient who underwent a Fontan procedure during the Glenn hospitalization, 25 (51.0%) completed the Fontan stage at a median age of 36.7 months (IQR 26.2-48.9 months) with 18 of them (72.0%) receiving a fenestration. In-hospital mortality for the Fontan procedure was 6/25 (24.0%). Twenty-eight patients had no additional surgery beyond Glenn stage in the PCCC. Fourteen of these patients were deemed not adequate surgical candidates based on the center's criteria, including hypoplastic branch pulmonary arteries (14.3%), extensive veno-venous collaterals (14.3%), sub-aortic obstruction (7.1%), pulmonary artery occlusion (21.4%), or elevated mPAP/PVR (42.8%) and one of them needed Glenn takedown. Of the 28 Glenn patients without additional reported congenital heart surgery, six are presumed alive, eight died, and the remaining 14 have no additional information beyond their last encounter in the PCCC (Figure 1).

We compared available cardiac catheterization hemodynamic data after the Glenn stage for patients with (N = 22) and without (N = 19) progression to the Fontan stage in PCCC registry (Table 4). Of those with complete hemodynamic measurements performed, patients who did not undergo Fontan had higher mPAP (median 15 mm Hg vs 11 mm Hg, P < .001) and had a higher TPG (6 mm Hg vs 5 mm Hg, P = .013).

3.2 | Cumulative long-term survival and comparison with controls

Long-term survival analysis over a median follow-up of 5.8 years (95% CI 1.3-15.6 years) and 407 patient-years follow-up was completed for 53 patients meeting criteria for PCCC-NDI-OPTN linkage, 47 of whom underwent a stage 1 procedure. No T21 patients received a transplant during the follow-up period. Conditioned on being discharged alive after a Stage I procedure, 1-, 5-, 10-, and

TABLE 1 Characteristics of the Trisomy 21 single ventricle cohort

	All Patients N = 118	Patients with identifiers N = 71	Patients without identifiers N = 47	P value
Male sex	64 (54.2)	37 (52.1)	27 (57.4)	.578
1st surgery by era				<.001
1982-1989	10 (8.5)	7 (9.9)	3 (6.4)	
1990-1999	51 (43.2)	44 (61.9)	7 (14.9)	
2000-2008	57 (48.3)	20 (28.2)	37 (78.7)	
Age category at 1st surgery				.209
Neonate ≤ 28 days	52 (44.1)	27 (38.0)	25 (53.2)	
Infant (29 days-1 year)	62 (52.5)	42 (59.2)	20 (42.5)	
Child (>1, <21 year)	4 (3.4)	2 (2.8)	2 (4.3)	
Single ventricle diagnosis				
Systemic right ventricle	3 (2.5)	8 (11.3)	4 (8.5)	.913
Systemic left ventricle	12 (10.2)	2 (2.8)	1 (2.1)	
Unbalanced CAVC[a]	97 (82.2)	58 (81.7)	39 (83.0)	
Other complex defect[b]	6 (5.1)	3 (4.2)	3 (6.4)	
Median age (months) at 1st surgery (IQR)	2.23 (0.43-5.39)	2.46 (0.46-5.91)	1.34 (0.29-4.60)	.147
In-hospital deaths at 1st surgery	28 (23.7)	17 (23.9)	11 (23.4)	1.000
Final physiology				.074
Stage 1	52 (44.1)	36 (50.7)	16 (34.0)	
Stage 2 (Glenn)	41 (34.7)	19 (26.8)	22 (46.8)	
Stage 3 (Fontan)	25 (21.2)	16 (22.5)	9 (19.2)	
Last vital status				
In-hospital deaths	56 (47.5)	34 (47.9)	22 (46.8)	1.000
Post discharge deaths (by NDI match)	21 (17.8)	21 (29.6)	—	
No NDI match (presumed alive)	16 (13.5)	16 (22.5)	—	
Unknown	25 (21.2)	—	25 (53.2)	

Notes: Given are numbers (*N*) and % (within parenthesis) for categorical variables, median, and interquartile range (IQR) for continuous variables. *P* value represents Chi-square test for categorical variables, Fisher's exact test for categorical variables with expected cell counts less than 5 or 2 × 2 comparisons, and Mann-Whitney *U* test for continuous variables.
[a]Dominant left ventricle 61.8%.
[b]Include: double outlet right ventricle, double inlet left ventricle, and Ebstein's disease.

TABLE 2 Surgical outcomes by staged physiology

	Procedures N = 200	Revisions[a] N = 12	In-hospital deaths N = 50	Post discharge deaths N = 33	Next stage N = 74	No follow-up N = 25
First stage	110	7 (6.4)	29 (26.4)	19 (17.3)	50 (45.4)	4 (3.6)
PA band	53	1 (1.9)	7 (13.2)	14 (26.4)	27 (50.9)	4 (7.5)
AP shunt	39	6 (15.4)	9 (23.1)	5 (12.8)	18 (46.1)	—
Norwood/DKS	18	—	13 (72.2)	—	5 (27.8)	—
Glenn	65	4 (6.1)	15 (23.1.)	8 (12.3)	24 (36.9)	14 (21.5)
Fontan	25	1 (4.0)	6 (24.0)	6 (24.0)	0	7 (28.0)

Note: Given are numbers (*N*) and % (within parenthesis) for categorical variables.
Abbreviations: PA, pulmonary artery; AP, aorto-pulmonary; DKS, Damus-Kaye-Stansel.
[a]Revisions include: AP shunt rescue (*n* = 2), Glenn (*n* = 1) or Fontan takedown (*n* = 1), AP shunt revision (*n* = 4), Glenn revision (*n* = 3), PA band revision (*n* = 1).

TABLE 3 Index operations during initial and subsequent admissions in PCCC

	Index procedure	In-hospital deaths
Initial admission	***N* = 118**	***N* = 29**
PA band[1,3]	45 (38.2)	6 (13.3)
AP shunt[2,4]	29 (24.6)	6 (20.7)
Glenn[5,6]	15 (12.7)	3 (20.0)
AP shunt followed by Glenn	2 (1.7)	0
Norwood procedure	13 (11.1)	8 (61.5)
CoA repair + PA band	7 (5.9)	0
DKS	5 (4.2)	5 (100)
DKS + Glenn	1 (0.8)	0
CoA repair + PA band, followed by Glenn	1 (0.8)	1 (100)
Subsequent admission	Index procedure	In-hospital deaths
	N = 92	*N* = 21
PA band	1 (1.1)	0
AP shunt	10 (10.9)	3 (30.0)
Glenn[a6]	43 (46.7)	5 (11.6)
DKS + Glenn	6 (5.4)	4 (66.7)
AV valve repair or replacement[8]	3 (3.3)	1 (33.3)
Atrial septectomy	1 (1.1)	0
Glenn takedown	1 (1.1)	1 (100)
Fontan procedure[7,9,10]	25 (27.1)	6 (24.0)
Subaortic stenosis repair	2 (2.2)	1 (50.0)

Note: Given are numbers (*N*) and % (within parenthesis) for categorical variables.
Abbreviations: AP, aorto-pulmonary; AV, atrioventricular; CoA, coarctation of the aorta; DKS, Damus-Kaye-Stansel; PA, pulmonary artery.
Some patients underwent additional procedures during the same admission including: PA band revision (*n* = 1),[1] AP shunt revision (*n* = 4),[2] pacemaker implantation (*n* = 1),[3] AV valve repair (*n* = 1),[4] tricuspid valve closure + septectomy (*n* = 1),[5] AP shunt rescue post Glenn (*n* = 2),[6] atrial septectomy (*n* = 1),[7] AP shunt (*n* = 1),[8] Fontan takedown (*n* = 1),[9] or Glenn followed by Fontan in the same admission (*n* = 1).[10]
[a]Including revisions (*n* = 3) of previously performed Glenn procedures.

15-year survival was 78.7%, 53.2%, 44.7%, and 34.9%, respectively (Figure 2A). Conditioned on being discharged alive after the Glenn procedure, 1-, 5, 10-, and 15-year survival was 89.7%, 62.1%, 51.7%, and 41.3%, respectively (Figure 2B). Finally, conditioned on being discharged alive after the Fontan procedure, 1-year survival was 91.7%, 5-year survival was 75.0%, and 10-year survival was 66.7% (Figure 2C). There was no difference in survival following the Fontan procedure between patients who underwent fenestrated Fontan compared to those with a non-fenestrated Fontan (*P* = .856). The median age at death for patients who underwent Glenn anastomosis as their final palliation was 3.0 years (IQR 0.9-7.4) and 5.2 years (IQR 2.6-11.4) for patients who underwent Fontan procedure (*P* = .190).

TABLE 4 Cardiac catheterization hemodynamics following Glenn procedure (*N* = 41)

	No Fontan	Fontan	
	***N* = 19**	***N* = 22**	***P* value**
SVO_2 (%)	52 (34-62)	60 (51.5-63.3)	.063
	N = 17	*N* = 22	
Mean PAP (mm Hg)	15.0 (13-16.8)	11.0 (9.8-13.3)	<.001
	N = 18	*N* = 22	
TPG (mm Hg)	6.0 (4.3-8.8)	5.0 (3.0-5.0)	.013
	N = 16	*N* = 22	
PVR (WU m^2)	2.6 (2.3-3.6)	2.4 (1.5-3.4)	.311
	N = 10	*N* = 15	

Notes: Given are median and interquartile range (IQR) for continuous variables. *P* value for Mann-Whitney *U* test.
Abbreviations: EDP, systemic ventricle end-diastolic pressure; PVR, pulmonary vascular resistance; SVO_2, mixed venous oxygen saturation; TPG, transpulmonary gradient.

Comparison of characteristics of 16 T21 Fontan patients who had long-term survival data with 55 Fontan patients without a known genetic anomaly and similar CHD during the same era is presented in Table 5. Patients without T21 were more likely to have complex SV anatomy, including unbalanced CAVC with pulmonary atresia or stenosis, transposition of the great arteries, or left-sided obstructive lesions. Patients with T21 were more likely than their counterparts without genetic anomaly to have a systemic LV than RV, but the two groups had similar pre-Fontan hemodynamics. Three patients in the control group without genetic anomaly underwent heart transplant after their Fontan procedure. Ten-year transplant-free survival following discharge after Fontan procedure was significantly lower for T21 patients compared to controls [66.7% (95% CI 33.7-86.0) vs 92.2 % (95% CI 80.4-97.0), *P* = .001] (Figure 2C); however, there was no significant difference between median age at death between the two groups (5.2 for T21 vs 5.5 years for controls, *P* = .739). Transplant-free survivors without genetic anomaly had a lower mPAP compared to non-survivors (*P* = .01), but the same comparison was not statistically different in the T21 group (Table 6).

3.3 | Causes of death

Causes of death, as reported by the death certificate, for 37 T21 patients who expired after discharge from the initial surgical procedure were primarily CHD-related (89.2%), with only four (10.8%) being unrelated to the underlying CHD or other cardiac causes (Table 7). NDI contributing causes of death revealed that cardiovascular causes other than CHD were identified in 67.6% of deaths, including pulmonary hypertension (18.9%), heart failure (24.3%), cardiac arrest (10.8%), and arrhythmia (10.8%). Non-CHD/non-cardiovascular contributing causes of death included T21 in 11/37 (29.7%), respiratory conditions in 14/37 (37.8%) of them (including respiratory failure in eight and pneumonia/other respiratory infection in six), while malignancy was involved in only one of the reported deaths.

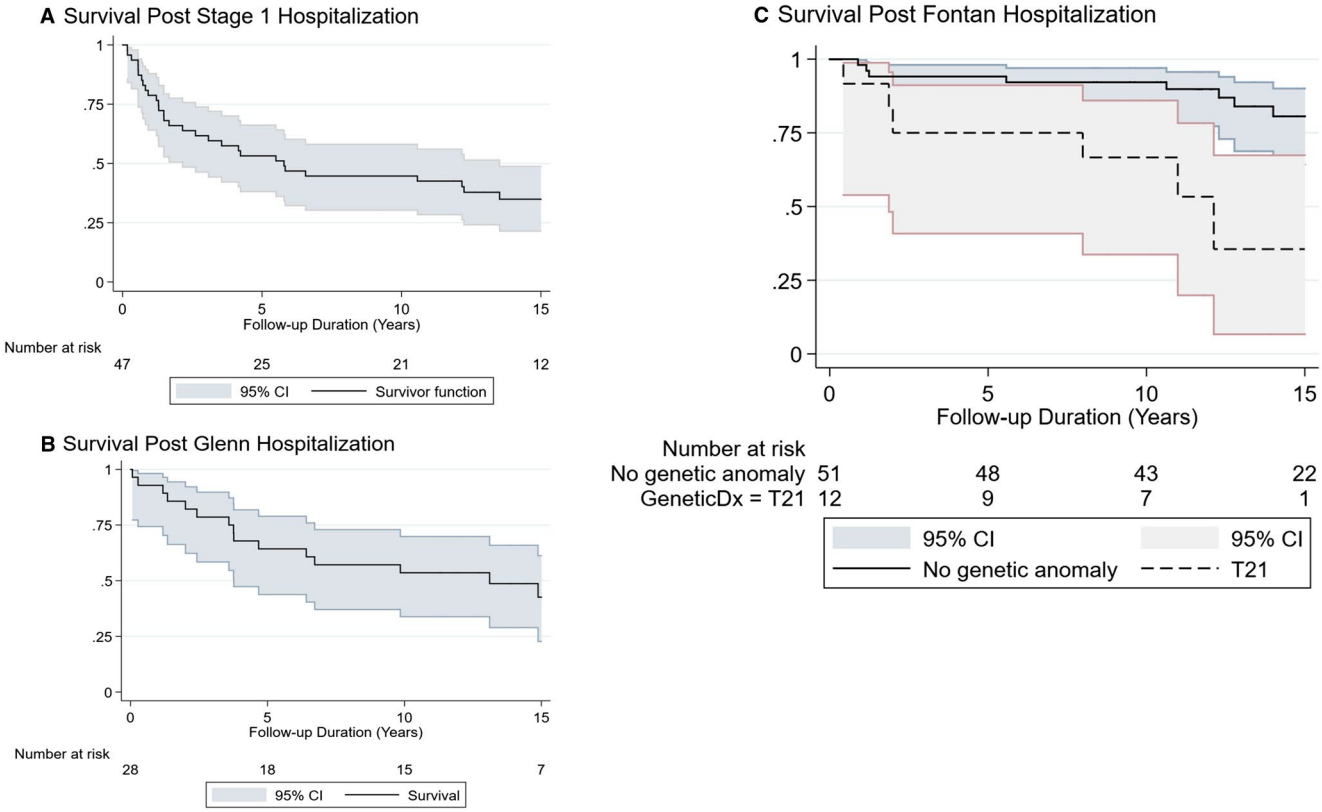

FIGURE 2 Kaplan-Meier transplant-free survival plot conditioned on hospital discharge: (A) after the Stage I procedure in Trisomy 21 patients with single ventricle physiology. (B) after Glenn procedure in patients with Trisomy 21 and single ventricle physiology, and (C) after Fontan procedure in patients with Trisomy 21 compared to controls without known genetic anomaly. CI, confidence interval; T21, Trisomy 21

4 | DISCUSSION

Large meta-analysis studies on Fontan outcomes have reported an overall in-hospital mortality of 8.3% (95% CI 5.0%-13.5%) and a pooled survival estimate of 88.4%, 85.7%, 84.1%, and 82% at 5, 10, 15, and 20 years, respectively.[14,15] However, these studies were not able to separately analyze patients with chromosomal abnormalities. Using the PCCC cohort and mortality data from the NDI, we recently reported that PCCC patients with SV anatomy had survival estimates of 84.1%, 82.7%, 80%, and 78.4% at 5, 10, 15, and 20 years, respectively.[11] As part of the same cohort, we now report the in-hospital and long-term survival for one of the largest series of patients with T21 following SV palliation.

A previous study of Fontan patients with T21 from the PCCC reported higher in-hospital and 30-day mortality following the Fontan procedure in T21 patients compared to non-syndromic controls.[9] The current study represents an extension of this prior PCCC report on T21 patients with SV for up to 10 years post Fontan and 15 years following initial procedure. Our study confirms previous reports[4,5,7-9] suggesting that for a selected group of patients with T21 survival is possible at the SV pathway despite increased risk for procedural mortality. It also adds 10-15 years of follow-up to the longest series of patients with T21 and SV physiology published by Colquitt et al.[7] Despite differences in era and methodology, survival in our cohort is comparable to Colquitt's study up to the 5 years of follow up covered by both studies.

This study identifies significantly decreased long-term survival following the Fontan procedure in patients with T21 compared to SV controls without a known genetic anomaly. It is interesting to note that the patients with T21 were more likely to have a morphologic LV, and the comparison group patients without genetic abnormality were more likely to have a morphologic RV, consistent with previous reports.[16,17] Despite the prevalence of less complex SV CHD and the predominance of LV morphology in the T21 group, survival following the Fontan was significantly shorter.

Elevated pulmonary artery pressure is known to complicate the course of patients without a dedicated subpulmonary ventricle[18] and is common in patients with T21 due to sleep disordered breathing.[19-21] Not surprisingly, our data highlight the importance of pulmonary vascular "health" for selecting T21 candidates for Fontan completion and the pre-Fontan hemodynamics indicate similar measures (mPAP, TPG, and PVR) with the control group. Despite similar starting hemodynamics at the time of the Fontan procedure, patients with T21 still experienced higher overall mortality than their euploidic counterparts, possibly due to a T21-specific morbidity. For example, in patients with T21, airway obstruction has been shown

TABLE 5 Comparison of characteristics between long-term Fontan survivors with T21 vs no known genetic anomaly

	T 21 *N* = 16	No genetic anomaly *N* = 55	*P* value
Clinical features			
Male Sex	7 (43.8)	25 (45.4)	1.00
Birth era (%)			
1990-1999	10 (62.5)	42 (76.4)	.339
2000-2003	6 (37.5)	13 (23.6)	
Systemic ventricle (%)			
Left ventricle	11 (68.7)	16 (29.1)	.020
Right ventricle	5 (31.3)	36 (65.5)	
Undetermined	0 (0)	3 (5.4)	
Single ventricle type (%)			<.001
Unbalanced CAVC	8 (50.0)	4 (7.3)	
Complex unbalanced CAVC[a]	7 (43.7)	48 (87.3)	
Complex tricuspid/pulmonary atresia[b]	0	3 (5.4)	
Hypoplastic left heart syndrome	1 (6.3)	0	
Fontan age (years)	3.0 (2.3-3.9)	3.1 (2.3-4.1)	.665
<2 years	3 (18.8)	7 (12.7)	.847
2-4 years	9 (56.2)	33 (60.0)	
>4 years	4 (25.0)	15 (27.3)	
Fontan type			
Extracardiac	11 (68.7)	34 (61.8)	.771
Lateral tunnel	5 (31.3)	21 (38.2)	
Fenestrated	11 (68.7)	36 (65.4)	1.00
Pre-Fontan hemodynamics			
SVO_2 (%)	62.0 (58.0-69.0)	64.5 (58.0-69.0)	.74
Missing (%)	1 (6.3)	5 (9.1)	
Mean PAP (mm Hg)	11.0 (10.0-14.0)	11.0 (8.5-13.0)	.62
<15 mm Hg (%)	12 (75.0)	44 (80.0)	.87
≥15 mm Hg	3 (18.7)	8 (14.5)	
Missing (%)	1 (6.3)	3 (5.5)	
EDP (mm Hg)	7.0 (5.0-10.0)	7.0 (6.0-9.0)	.78
Missing (%)	1 (6.3)	2 (3.6)	
TPG (mm Hg)	5.0 (3.0-6.0)	5.0 (4.0-6.0)	.79
Missing (%)	1 (6.3)	7 (12.7)	
PVR (W sUm^2)	1.6 (1.5-2.4)	1.8 (1.3-2.3)	.52
Missing (%)	3 (18.7)	14 (25.4)	

Notes: Given are numbers (*N*) and % (within parenthesis) for categorical variables, median, and interquartile range (IQR) for continuous variables.
Abbreviations: CAVC, common atrioventricular canal; EDP, systemic ventricle end-diastolic pressure; PVR, pulmonary vascular resistance; SVO_2, mixed venous oxygen saturation; TPG, transpulmonary gradient.
Chi-squared and Fisher's exact tests were used to compare categorical variables and Wilcoxon rank sum test to compare continuous variables.
[a]Unbalanced CAVC + transposition of the great arteries and/or pulmonary stenosis/atresia or left sided obstruction.
[b]Tricuspid or pulmonary atresia + transposition of the great arteries.

to increase with age and body mass index and as a result, pulmonary function may deteriorate over time.[22] Therefore, hemodynamic markers measured at the pre-Fontan evaluation may not necessarily predict the success of a patient with T21 in the Fontan pathway. Children with T21 have been reported to have an incidence of sleep disordered breathing from 66% to 97%,[19,20,22] compared to 1%-4% in children without T21.[23] The increased prevalence of sleep disordered breathing in children with T21 may also explain the differential long-term survival between patients with T21 and their euploidic counterparts. Preventative education and screening and treatment of obstructed breathing in T21 patients may be critical for maximizing the potential of the Fontan circulation. Adjunctive treatment

TABLE 6 Comparison of pre-Fontan hemodynamics by survival outcome[a] in patients with Trisomy 21 and patients with no known genetic anomaly

	Deaths	Alive	
Trisomy 21	***N* = 8**	***N* = 8**	***P* value[b]**
Fontan age (Years)	3.2 (2.3-3.9)	3.0 (2.2-3.8)	.88
SVO_2 (%)	64.0 (59.0-70.5)	61 (53.0-64.0)	.40
Mean PAP (mm Hg)	12.5 (9.0-15.0)	11 (10.0-12.0)	.46
TPG (mm Hg)	4.5 (3.0-7.0)	5.0 (4.0-5.0)	1.000
PVR (WU m^2)	1.5 (1.5-3.4)	1.9 (1.6-2.4)	.44
No known genetic anomaly	***N* = 8**	***N* = 48**	***P* value**
Fontan age (Years)	2.6 (2.0-4.2)	3.3 (2.5-4.1)	.26
SVO_2 (%)	58.0 (54.0-67.0)	65.0 (58.0-69.0)	.26
Mean PAP (mm Hg)	13.5 (12.0-15.0)	10.5 (8.0-13.0)	.01
TPG (mm Hg)	5.0 (4.0-6.0)	5.0 (4.0-6.0)	.73
PVR (WU m^2)	2.0 (1.8-2.2)	1.8 (1.2-2.3)	.63

Note: Median and interquartile range are given for all continuous parameters.
Abbreviations: EDP, systemic ventricle end-diastolic pressure; PVR, pulmonary vascular resistance; SVO_2, mixed venous oxygen saturation; TPG, transpulmonary gradient.
[a]Follow-up time is restricted to 8.3 years, which is the longest follow-up period available for all subjects.
[b]Wilcoxon rank sum test to compare continuous variables.

TABLE 7 Underlying and contributing remote causes of death for T21 patients after surgical palliation for single ventricle

Underlying cause of death		Contributing causes of death	
Cause	***N* (%)**	**Cause**	***N* (%)**
CHD	33 (89.2)	**CHD**	28 (75.7)
CVD	0	**CVD**	25 (67.6)
		Heart failure	9 (24.3)
		Pulmonary hypertension	7 (18.9)
		Cardiac arrest	4 (10.8)
		Arrhythmia/Conduction disorder	4 (10.8)
		Cerebrovascular Disease	3 (8.1)
		Thromboembolism	2 (5.4)
		Cardiomyopathy	2 (5.4)
		Endocarditis	1 (2.7)
		Other CVD	4 (10.8)
Non-CHD/Non-CVD	4 (10.8)	**Non-CHD/Non-CVD**	26 (70.3)
Respiratory conditions	1 (25.0)	Trisomy 21	11 (29.7)
Neurological conditions	1 (25.0)	Respiratory conditions	14 (37.8)
Gastrointestinal causes	1 (25.0)	Renal failure	3 (8.1)
Trisomy 21	1 (25.0)	Shock	3 (8.1)
		Gastrointestinal causes	3 (8.1)
		Leukemia	1 (2.7)
		Other	10 (27.0)

Note: Frequency (and percent within parenthesis) are given for categorical variables.
Abbreviations: CHD, congenital heart disease; CVD, cardiovascular disease.

with pulmonary vasodilators[24,25] may be important to improve the longevity of the Fontan circulation in patients with T21.

Other mechanisms for increased mortality in our cohort include heart failure, arrhythmias, and pneumonias which may reflect differences in cardiovascular reserve, inherent vulnerability for respiratory infections, and systemic inflammatory responses reported by other investigators.[9,26-29] Overall, our findings related to late causes of death are consistent with other studies investigating long-term

mortality following congenital heart surgery and Fontan.[30-33] These findings are consistent with the hypothesis that patients with T21 are more susceptible to and less able to compensate for the adverse effects of SV physiology.

In our cohort, only 21.2% of the T21 SV cohort reached a Fontan procedure with almost 50% of them determined to be ineligible because of anatomic or hemodynamic factors. Given the high-risk nature of patients with T21 and SV physiology, careful assessment of pre-Glenn and pre-Fontan hemodynamics, management of obstructive respiratory disease, pharmacological optimization of PVR, and investigation and correction of any significant residual anatomic abnormalities are warranted. In addition, our study did not find a significant survival benefit in patients who underwent Fontan, compared to patients who remained at Glenn physiology. The risks of additional surgery must be carefully weighed against the potential benefits, especially in patients with borderline hemodynamics. Individual patient factors such as activity level, functional status, and family preference should also be considered.

The major strengths of this study are the multi-institutional cohort and long-term follow-up. The linkage of PCCC clinical data with the "gold standard" NDI offers important information about expected long-term outcomes for this cohort of unique patients. However, our study also has some notable limitations. Despite the relatively large cohort size, the sample size is still limited for meaningful analysis of risk factors associated with long-term outcomes. Since some T21 patients with SV may not have been offered interventions, our reported survival applies only to T21 patients who underwent intervention for their CHD. Patients lacking follow-up data after their initial palliation in PCCC may have undergone subsequent procedures at non-PCCC participating centers. We report intention-to-treat outcomes based on the initial intervention; however, it is possible that some patients with unknown outcomes eventually underwent biventricular, 1½ ventricle repair, or further SV palliation. It is also possible that some patients in the Fontan comparison group may have also had heterotaxy that was not coded in the procedural reports.

5 | CONCLUSIONS

The PCCC-NDI-OPTN linkage provides new insights on the expected outcomes of patients with T21 and SV physiology, a small and uniquely high-risk group. Data from this large, multi-institutional combined dataset highlight the challenges in this population at every stage of the SV pathway. Patients with T21 and SV physiology have reduced long-term survival compared to peers without genetic anomalies. However, for carefully selected patients, long-term survival following SV palliation is possible.

Individual health care providers may care for small numbers of patients with T21 and SV CHD, but the results of this study quantify long-term outcomes for patients with this rare combination of conditions and provide a basis for discussion with affected patients and families, as well as comparison to future outcomes. Future long-term outcomes in this group of patients may be improved by aggressive management of the pulmonary hemodynamics by addressing airway obstruction and hypoventilation in combination with pulmonary vasodilators now available.

DISCLAIMER

The data reported here have been supplied by UNOS (United Network for Organ Sharing) as the contractor for the Organ Procurement and Transplantation Network (OPTN). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the US Government.

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CONFLICT OF INTEREST

The authors have no conflicts of interest or financial disclosures relevant to this article to disclose.

AUTHOR CONTRIBUTIONS

Study concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article, statistics: JKP
Study concept/design, data interpretation, drafting article, critical revision of article, approval of article, funding secured by: SPS, LKK
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